Remarks

The following remarks are provided in further support of the Claims.

Present Status of the Claims: Claims 1-7 are pending.

Rejections:

Rejection Under 35 U.S.C. §112

Claims 1-6 are rejected under 35 U.S. C. §112 second paragraph as being indefinite, vague, and confusing for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Claims 1-5 are rejected under 35 U.S. C. §112 first paragraph because the specification does not reasonably provide enablement for a person skilled in the art to make and use the invention commensurate with in scope with these claims.

Claims 6 and 7 are rejected under 35 U.S. C. §112 first paragraph as failing to comply with the written description requirement.

Rejection Under 35 U.S.C. §102

Claims 6 and 7 are rejected under 35 U.S.C. §102(b) as being anticipated by the abstract of Uhal et al. (1991) or the paper of Luther et al. (1996).

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I. DISCUSSION - 35 U.S.C. §112

The Office rejected claims **1-6** under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1: The Office asserts that the metes and bound of **claim 1** cannot be determined due in part to the existence of a phrase appearing after the period indicating the end of **claim 1**. This phrase has been deleted from **claim 1** and the invention concept embodied in the extra phrase has been clarified and incorporated as a additional independent **claim 8** and dependent **claim 9**.

The lack of clarity in the original **claim 1** with regard to how the first method step of determining the reference laser wavelength of the laser biocavity when only fluid without cells is present has been removed by the alteration of the wording of the claim while still encompassing the same inventive concept. We have more explicitly described the relationship between the laser wavelength without a cell in the biocavity and the shift in the laser wavelength when a cell is in the biocavity. While the step of categorizing the phase of a cell using the wavelength shift was inherent in the invention, we have explicitly included it in **claim 1** to make it more clear how the percentage of cells in the G2 phase is determined with this invention.

Claim 2: The Office asserts that **claim 2** is vague and indefinite in the recitation of "range where G2 phase cells are expected" and that the metes and bounds of **claim 2** are unclear without specific limitations for said range. The lack of clarity has been

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removed by amendment of the wording of the claim while still encompassing the same inventive concept. The claim language now specifically states that the wavelength shift corresponds to the laser wavelength of the biocavity when a cell in the G2 phase is present in the biocavity. The language has been amended to clarify proper antecedent relationships for "wavelength" and "wavelength shift".

Claim 3: The Office asserts that **claim 3** is vague and indefinite in the recitaiton of "range where G2 phase cells are expected" and "range where G1 phase cells are expected" and that the metes and bounds of **claim 3** are unclear without specific limitations for said range. The lack of clarity has been removed by amendment of the wording of the claim while still encompassing the same inventive concept. The claim language now specifically states that the wavelength shift corresponds to the laser wavelength of the biocavity when a cell in the G2 phase is present in the biocavity or to the laser wavelength of the biocavity when a cell in the G1 phase is present in the biocavity. The language has been amended to clarify proper antecedent relationships for "wavelength" and "wavelength shift".

Claims 4-6: The Office asserts that **claims 4-6** are vague and indefinite in the recitation of "wavelength shift" without a recitation of the relative point from which said shift is measured. The lack of clarity has been removed by amendment of the wording of the claims while still encompassing the same inventive concept. The language has been amended to clarify proper antecedent relationships for "wavelength" and "wavelength shift".

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Claims 4: The Office asserts that **claim 4** is vague and indefinite as it is not clear how the determination of the wavelength shift of the biocavity when a cell passes through or how the measurement of the fluid filled biocavity affects the determination of the phase of the cell. The manner in which the measurment of the optical resonance wavelength of the biocavity relates to the phase of the cell is described in the specification on pages 6 through 8. Briefly, when a liquid is flowed through a laser microcavity, of which the biocavity is an example, the wavelength corresponding to optical resonance, which is seen as a sharp peak in the emission spectrum of the laser, is determined by the roundtrip light path in the microcavity. The wavelength of light that corresponds to an integral number of light wavelengths in the microcavity (the condition producing optical resonance) depends on the refractive index of the material within the optical cavity. In the absence of a cell, the refractive index that determines the peak emission wavelength is the refractive index of the fluid. This provides the reference wavelength against which a wavelength shift is measured when a cell is present in the laser microcavity. When a biomolecular concentration such as a cell is in the cavity, there is a change in the refractive index that is determined by the concentration of biomolecules in the cell in the fluid. This change in the refractive index changes the wavelength corresponding to optical resonance and produces a spectral wavelength shift in the sharp peaks of the emission spectrum of the biocavity laser. In short, the change in the biomolecular concentration changes the refractive index of the fluid, which in turn changes the optical resonance wavelength of the biocavity laser and shifts the wavelength of the strong peaks in the emission spectrum of the laser. This makes the

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spectral wavelength shift a direct measurement of the average biomolecular concentration in the laser microcavity. The biomolecular concentration is different in different phases of the cell cycle, so measuring the biomolecular concentration by measuring the change in optical resonance wavelength (the wavelength shift) provides a measurement of which phase a cell within the laser microcavity is in during the optical measurement. The clarity of **claim 4** has been improved by amendment of the wording of the claim while still encompassing the same inventive concept.

Claim 5: The Office asserts that **claim 5** is vague and indefinite in the recitation of "distinct values of wavelength shift" and that it is unclear what qualifies a numerical value to be a "distinct" vs. an indistinct value. The Office also asserts that **claim 5** is vague and indefinite in the recitation of "increased number of cells in G2 phase" with out an indication of what this increase is in comparison to. The Office also asserts that **claim 5** is vague and indefinite in the recitation of "the number of data points" without an indication of the parameters of said data points. The lack of clarity has been removed by amendment of the wording of the claim while still encompassing the same inventive concept.

Claims 6 and 7: The Office asserts that it is unclear how the recitation of "determining from the wavelength shift the percentage of cells having a concentration greater than the concentration of a normal cell" in **claim 6** relates to the method objective of determining cell concentration. In accordance with the information found in the specification on p. 7, line 16 through p. 8, line 4, the term "concentration" in **claim 6** has

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been clarified by the addition of an adjective to become "biomolecular concentration" to indicate that the "concentration" of the claims is not the concentration in terms of the number of cells per unit volume but rather the concentration of biomolecular mass in a fixed cell volume within an individual cell, which is an measurement of the phase of a cell.

Further the Office asserts that the recitation of "the percentage of cells" and "a normal cell" in **claims 5** (we assume this to be typographical error with **claim 6** being the proper subject of this section of the office action) **and 7** appears to have no antecedent basis within the claims which are drawn to the determination of cell concentration within a biocavity laser. The Office asserts that said determination would yield only the number of cells per unit volume. The Office questions what is meant by "percentage of cells having a concentration greater than the concentration of a normal cell" in relation to determining the number of cells per unit volume cannot be construed from the claim language. The term "concentration" has been clarified by the addition of the adjective "biomolecular, as explained in the preceeding paragraph. The lack of clarity with respect to "concentration" has been removed by amendment of the wording of the claims. Additionally, **claim 7** has been amended to describe more clearly the method whereby the biomolecular concentrations of the plurality of cells may be used to achieve the method objective.

Claim 7: The Office asserts that that **claim 7** is vague and indefinite in the recitation of "predetermined amount" and that without specific limitations the metes and bounds of the claims cannot be determined. The phrase, "predetermined amount" has been

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deleted from the claim and the lack of clarity has been removed by amendment of the wording of the claim.

Claims 1, 4, and 5: The Office asserts that **claims 1, 4, and 5** are vague and indefinite as it is unclear if the multiple recitations of wavelength shift refer to the same measured parameter. The lack of clarity has been removed by amendment of the wording of the claims while still encompassing the same inventive concept.

Claims **1-5** are rejected under 35 U.S. C. §112 first paragraph because the specification does not reasonably provide enablement for a person skilled in the art to make and use the invention commensurate with in scope with these claims.

Claims 1-5: The Office asserts that **claims 1-5** are not enabling for a person skilled in the art to make and use the invention commensurate in scope with the claims. The Office states that the specification is enabling for a method of determining the phase of cells in the cell cycle for a homogeneous population of cells but asserts that it does not provide enablement for a method of determining the phase of cells in the cell cycle or a heterogeneous population of cells. The Office asserts that the specification is not enabling for detection of cancer from a sample taken from an in-situ tumor or for the determination of the phase of cells in the cell cycle from a sample taken from an in-situ tumor. The Office asserts that global analysis of the cell cycle in a sample that is a mixture of different cell types does not provide direct information on the proliferation of each of the different subpopulations of cells present in the sample. The Office points out

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that the laser spectrum of a range of different tumor cells derived from a heterogeneous cell sample taken from a patient would be complex.

The complexity of the laser spectrum from each type of cell is an advantage for identifying both the cell type and phase of the cell cycle for a particular cell type originating in a heterogeneous sample using this present invention. It is customary in molecular spectroscopic analysis of heterogeneous samples to employ the simultaneous behavior of a number of spectral wavelengths originating from the same molecule to distinguish between the different individual molecular constituents of the heterogeneous sample. Similar standard analytical approaches can be applied to the analysis of the spectral information measured for individual cells in this present application. This present patent application incorporates by reference Gourley, U.S. Pat. No. 5.793,485, which describes a method employing the biocavity laser to measure the optical spectra of cells and to identify the particular type of cell by analyzing the wavelength information of the cell with respect to the laser wavelength shift, the laser mode separation, and the intensity. This is described from column 23 lines 24-60 and illustrated in Figures 12 and 13 of '485. By performing an analysis of the spectral data measured by the present invention in multidimensional coordinate space, identification of both cell type and phase is possible for a plurality of cells. Only 3 dimensions of data are shown in the cluster analysis illustrated in Fig. 13 of '485 but higher-dimensional cluster analysis is standard in the art of spectral interpretation, with higher-dimensional clusters increasing the level of certainty of the identification. Standard use of cluster analysis will allow the proper identification and counting of the different types of cells and of the phase in the cell cycle to which each cell corresponds.

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The rejection by the Office of **claim 5** with the phrase "number of data points grouped about distinct values of wavelength shift" has been addressed by amendment of the claim.

Claims **6 and 7** are rejected under 35 U.S. C. §112 first paragraph as failing to comply with the written description requirement.

The Office asserts that **claims 6 and 7** fail to comply with the written description requirement because the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. The Office further asserts that the claims encompass a genus of biocavity lasers while the specification of this application only provides a written description of a laser cavity wherein one surface is a semiconductor and, therefore, does not describe other possible materials required to represent a genus of biocavity lasers. However, this present application incorporates by reference the patent of Gourley, U.S. Pat. No. 5,793,485, which state in the description of the gain media of the biocavity (column 5 lines58 through 65): "The types of gain media 18 that can be used for practice of the present invention include gas, organic dye, solid state, and semiconductor gain media. Vertical-cavity surface-emitting semiconductor laser as shown in Figs. 3a and 3b and Fig. 19 are especially well-suited for forming, at least in part, the resonant optical cavity of the present invention, and for providing optical gain for generating the spontaneous emission or lasing light beam" (numbers refer to labels in Fig. 1 of '485). Thus, the invention is not restricted to use of a semiconductor laser only but encompasses a range of other possiblematerials; the applicant is in fact in possession of a genus of biocavity lasers. Therefore, the written

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description requirement has been met and **claims 6 and 7** are suitable for allowance as amended to improve the clarity of the wording of the claims.

II. DISCUSSION - 35 U.S.C. §102

Claims 6 and 7 are rejected under 35 U.S.C. §102(b) as being anticipated by the abstract of Uhal et al. (1991) or the paper of Luther et al. (1996).

The Office asserts that **claims 6 and 7** are rejected under §102(b) based on prior publications by Uhal et al. and Luther et al. The specifics are addressed below.

The Office asserts that the abstract of Uhal (1991)disclosing the quantization of a fraction of G2/M phase cells in pneumonectomized rats versus normal rats serves as prior art under §102(b). The method of Uhal and Rannels is based upon the chemical labeling of cells with bromodeoxyuridine (BrdU) for at least one hour to permit incorporation of the labeling BrdU in the nDNA of the cells that were to be subsequently analyzed by fluorescence microscopy. Our invention does not require any labeling step to permit identification of the phase in the cell cycle. Consequently, the abstract of Uhal does not constitute prior art under 35 U.S.C. §102(b).

The Office asserts that the disclosure of Luther et al. (1996)of the resolution of G2 vs. G1 cells, page 276 fig. 3 of Luther, by means of laser scanning cytometry serves as prior art under §102(b). The method of optical identification of the cell phase in Luther et al. is an optical microscope that measures fluorescence and light scattering of cells on a microscope slide. The cells were fixed and stained before measurement of the fluorescence. In contrast, our invention does not require staining of the cells before

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measurement nor does it rely upon the fluorescence of the cell for the identification of the phase. Our invention is based upon the change in the refractive index of the laser biocavity, of which the cell being analyzed is a part, to produce a shift in the output wavelength of the biocavity laser. Consequently, the paper of Luther and Karnentsky does not constitute prior art under 35 U.S.C. §102(b).

Conclusion

Applicants have responded to each and every objection and rejection, and urge that Claims **1-9** as presented are now in condition for allowance. Applicants request expeditious processing to issuance.

Respectfully submitted,

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